Clin. Lab. 2024;70:XXX-XXX

ORIGINAL ARTICLE

Cytokines and Other Laboratory Parameters of Hospitalized COVID-19 Patients that Predict Intensive Care Unit Admission

Necati Cakir [1], Eren Gozke [2], Semiha C. Ekinci [3], Sinem A. Isik [3], Sibel Osken [1], Zeynep Kaya [1], Eylem A. Guner [1], Feyza Ak [1], Hanife A. Yazicilar [4], Haluk Kilic [4], Burcu S. Anil [5], Muhammet Ozgul [5]

[1] *Department of Rheumatology, FSM Training and Research Hospital, University of Health Sciences, Istanbul, Turkey*
[2] *Department of Neurology, FSM Training and Research Hospital, University of Health Sciences, Istanbul, Turkey*
[3] *Department of Infectious Disease, Sultan Abdulhamid Han Training and Research Hospital, University of Health Sciences, Istanbul, Turkey*
[4] *Department of Microbiology, FSM Training and Research Hospital, University of Health Sciences, Istanbul, Turkey*
[5] *Department of Radiology, FSM Training and Research Hospital, University of Health Sciences, Istanbul, Turkey*

SUMMARY

Background: **This study aimed to investigate the roles of cytokines and other laboratory parameters in determining the need for intensive care in COVID-19 patients.**
Methods: **This is a retrospective observational study. Demographic, clinical, and laboratory parameters of the patients were evaluated. Thirteen cytokines were measured along with baseline laboratory tests at admission and at 48-hour intervals: IL-1β, IFN-α, IFN-β, TNF-α, MCP-1, IL-6, IL -8, IL-10, IL-2p70, IL-17A, IL-18, IL-23, and IL-33.**
Results: **COVID-19 was confirmed by PCR in 116 hospitalized patients. The mean age was 55.3 ± 16.4 years. Seventy-four (63.8%) of the patients were male and 42 (36.2%) were female. Twenty-two (18.9%) patients (16 male, 6 female) were transferred to the intensive care unit. A significant increase in white blood cell (WBC), neutrophil (Neu) and lymphocyte (Lym) counts, Neu/Lym ratio (NLR), lactate dehydrogenase (LDH), INR (international normalized ratio), activated prothrombin time (aPTT), D-dimer (D-D), troponin (Trop), Pro-BNP (BNP), procalcitonin (PCT), ferritin (Fer), and alanine aminotransferase (ALT) values were observed in those requiring intensive care. A significant decrease was found in albumin (Alb) levels and Lym counts. Alb levels appeared to be protective against admission to intensive care. Except for IFN- α, IL-23, and IL-33, the baseline values of other cytokines were above the threshold values. MCP-1 and IL-6 were higher in patients requiring intensive care.**
Conclusions: **High NLR and LDH and low Alb levels, especially with an increase in MCP-1 and IL-6, were found to be the best predictors of a serious COVID-19 infection.**
(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2024.240109)

Correspondence:
Eren Gozke
Department of Neurology
FSM Training and Research Hospital
University of Health Sciences
Istanbul
Turkey
Email: egozke@hotmail.com
ORCID: 0000-0001-6175-0647

Manuscript accepted May 19, 2024

KEYWORDS

COVID-19, cytokines, intensive care

INTRODUCTION

Human infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 - previously named 2019-nCoV) was first reported in late December 2019 in Wuhan, China [1]. SARS-CoV-2 is the third coronavirus to cause severe respiratory illness in humans, known as coronavirus disease 2019 (COVID-19),

after SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV) [2].
The clinical presentation of the COVID-19 ranges from a self-limiting, mild illness to multiple organ failure and death [3-5]. The most typical signs at disease onset are fever, sore throat, dry cough, fatigue, myalgia, and dyspnea [6-8]. In some studies, the rate of referral to intensive care unit varied between 23.6 - 26.1%, and the mortality rate was recorded between 4.3-12% [8-10]. Age, gender, ethnicity, geography, the health systems of the patients' country, and the presence of comorbidities affect the severity and fatality [11,12].
The causal relationship between pathogenicity or disease severity and biomarkers is still not very clear. Previous studies show that hematological manifestations of COVID-19 include blood count abnormalities, especially lymphopenia and neutrophilia, which have prognostic significance. The neutrophil-to-lymphocyte ratio (NLR) has been confirmed as a potential predictor for critical illness [13-15]. A study about NLR values reported an area under receiver operating characteristic curve of 0.849 (95% CI: 0.707 to 0.991) [15]. Additionally, hyperferritinemia and elevated LDH are linked to higher mortality [16]. Beside these, there is a lot of proof that COVID-19 is linked to a specific coagulopathy that is defined by raised D-D levels and a higher risk of thrombotic events [16-17].
Among the proinflammatory cytokines, fifteen cytokines, namely M-CSF, IL-10, IFN-α2, IL-17, IL-4, IP-10, IL-7, IL-1ra, G-CSF, IL-12, IFN-γ, IL-1α, IL-2, HGF, and PDGF-BB, were found to be strongly associated with lung injury [18].
It had been reported that COVID-19 incidence and mortality rates show regional differences within a country and between the countries, even at different times in the same population [19]. Understanding the COVID-19 profile in each nation will aid in limiting the illness and in developing appropriate policies and methods to deal with any ensuing waves [11]. Therefore, we aimed to describe epidemiological, clinical, and laboratory parameters, treatment, and outcomes of patients confirmed to have COVID-19 infection and aimed to compare the clinical features between ICU and non-ICU patients in a Turkish cohort of COVID-19 infected patients. Data for this study had been collected before vaccination was available.

MATERIALS AND METHODS

We conducted a retrospective observational study using data collected from the confirmed COVID-19 patients in an affiliated university hospital of 505 beds, in Istanbul, Turkey. Most patients had a computed tomography of the chest at the time of admission.
Since this study was conducted during the Covid-19 pandemic, the only approval was obtained from the Ministry of Health (2020-05-05T11_13_02), in accordance with the current legislation at that time.

All patients were diagnosed by reverse transcription-polymerase chain reaction method (RT-PCR), using nasopharyngeal swabs. The epidemiological, clinical, laboratory, and radiological features observed upon admission and throughout treatment, along with the clinical outcomes of these patients during their hospital stay, were obtained from the medical record system.
Peripheral blood was obtained from all patients on admission. The laboratory tests included:1) routine blood counts: hemoglobin (Hb), white blood cells (WBC), neutrophils (Neu), platelets (Plt), and lymphocytes (Lym); 2) coagulation tests: international normalized ratio (INR), prothrombin time (PT), active prothrombin time (aPTT) and D-dimer (D-D), and fibrinogen (Fib); 3) inflammatory markers: C- reactive protein (CRP), ferritin (Fer), procalcitonin (PCT), and lactate dehydrogenase (LDH); 4) liver function tests: ALT, AST, albumin (Alb), and alkaline phosphatase (AP) level; 5) renal function tests: creatinine, blood urea, and estimated glomerular filtration rate (GFR); 6) electrolytes: sodium (Na), potassium(K), and calcium (Ca); and 7) cardiac injury tests: troponin (Trp) and pro-PNB (BNP). The Lym value, representing the minimum lymphocyte count observed in each patient throughout the entire course, was documented. Similarly, the Neu value, indicating the neutrophil count obtained from the concurrent blood sample of each patient. The Neu/Lym ratio (NLR) value of each patient was calculated accordingly [15].
Approximately 4 - 5mL of fresh blood samples were taken into two separate tubes, one with and the other without anticoagulant. The blood samples were separated by centrifugation at 2,500 rpm for 10 minutes at 4°C as necessary and were immediately stored at -80°C until analysis.

Cytokine analyses

Serum samples were analyzed for IL-1β, IFN-α2, IFN-γ, TNF-α, MCP-1, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33 by using LegendPlex Human Inflammation Kit (Biolegend, USA) according to the manufacturer's instructions. Samples were run under Attune NxT Focusing Flow Cytometer (Thermo Scientific, USA). The instrument was calibrated at the means of FSC, SSC, and PMT voltages by calibration beads provided with the kit. 20,000 events were collected in FSC x SSC plot, and beads were classified and reported with APC x PE plot. Generation of standard curves and analysis of samples were done using LegendPlex Data Analysis Software v.8.0 (Biolegend,USA).

Statistical analyses

Statistical analyses were done by GraphPad Prism v.8.0 (GraphPad Software, USA). Mann Whitney U and General Linear Model-Repeated Measures ANOVA tests were used. Comparison of serum cytokine levels between days of sample collection was done with Kruskal-Wallis Test. Multivariate logistic regression analysis was carried out to predict the patient admission to ICU.

ROC curve analyses were used to assess for the diagnostic power of laboratory variables.
This study was conducted in accordance with the Declaration of Helsinki.

RESULTS

The mean age of the subjects was 55.3 ± 16.4 years. There were 74 (64%) males and 42 (36%) females. Twenty-two (18.9%) patients (6 female, 16 male) were transferred to ICU during hospitalization, 8 (6.9%) had died (2 female, 6 male), all in ICU. The mean time from symptom onset to death was 22 ± 7.8 days. The mean length of stay of the patients in the ward was 9.3 ± 4.7 and the mean time of stay in the ICU was 11.6 ± 9.4 days.

Symptoms on admission

The most common symptoms were fever 41 (35%), cough 39 (33.6%), shortness of breath 37 (31.8%), and malaise-fatigue 21 (18%) (Table1). The cough was mainly dry with no hemoptysis. The other symptoms were diffuse pain and myalgia 14 (12%), headaches 10 (10.3%), nausea and vomiting 10 (8.6%), loss of smell and taste 7 (6%), diarrhea 7 (6%), chest pain and feeling of chest pressure 5 (4.3%), sore throat 4 (3.4%), loss of appetite 4 (3.4%), stroke 3 (2.6%), confusion 1 (0.8%), nasal congestion 1 (0.8%), and abdominal pain 1 (0.8%). Fifteen (13%) of the patients did not report any symptoms but those who have been in contact with patients and whose COVID tests were positive (Supplementary Table 1).

Comorbidities on admission

In total, 73 (62.9%) of the patients reported at least one comorbidity, 43 (371%) had none. The most common comorbidities were hypertension 30 (27%) and diabetes mellitus 29 (26%) (Supplementary Table 1).

Laboratory values on admission

The blood counts of patients on admission showed leukopenia in 15(13.1%), leukocytosis in 13 (11.3%), neutropenia in 6 (5.1%), neutrophilia in 30 (25.6%), lymphocytopenia in 72 (68%), lymphocytosis in 9 (0.8%), NLR (> 5) in 72(62 %), thrombocytopenia in 17 (14.6%), and thrombocytosis in 7 (6%) of the patients. On admission, CRP levels in 84 (73%), LDH in 43 (37%), ALT in 40 (34.7%), AST in 27 (23.5%), Fer in 63 (54.7%), D-D in 58 (50%), Fib in 84 (73%), PT in 34 (29.5%), troponin in 6 (5.2%), and creatinine levels in 13 (11.3%) of the patients were increased, while Alb levels were decreased in 57 (49%) of the patients (Supplementary Table 2).
The patients were divided into two groups, as those who needed to be in the intensive care unit (ICU) and those who did not (non-ICU). On admission, the hematological and biochemical findings of the patients were compared by dividing them into these two groups retrospectively. The common laboratory indicators, such as Lym, Neu, NLR, CRP, LDH, PCT, Fib, and D-D, from 116 patients were compared between the ICU and non-ICU patients (Supplemantary Table 3).
WBC counts, NLR values, ALT, LDH, and PNB levels were significantly increased in ICU patients compared to non-ICU patients. While there was a significant increase in the number of neutrophils, the lymphocyte counts and albumin levels were less among the ICU patients. There was no difference between the groups in terms of Fib levels, but D-D, INR, PT, and Trp levels were higher in ICU patients. There was no significant difference between CRP values, but Fer averages were higher in ICU patients. Among the 103 patients in whom PCT levels were available, 61% of the patients had levels higher than normal values (> 0.05 ng/mL). PCT levels increased more in ICU patients (Supplementary Table 3).
Although total WBC, Neu and Lym counts, NLR, ALT, LDH, Fer, D-D, INR, PT, APTT, Trp, BNP, and PCT were significantly increased among the ICU patients as compared to the non-ICU patients, Alb was significantly decreased in the latter group. With multivariate logistic regression analyses, the results that had the highest odds ratios were: NLR (OR: 1.136, p: 0.045, 95% CI [1.003 - 1.287]), LDH (OR: 1.003, p: 0.032, 95% CI [1.000 - 1.005]), and Alb levels protective against being admitted to ICU (OR: 0.222, p: 0.025, 95% CI [0.06 - 0.825]). Given the importance of age for COVID-19 infection, the model was corrected for age. However, there was no significant variation.
The receiver operating charestiristic (ROC) curve analysis was performed to determine the predictive values of selected parameters for referral to intensive care unit (Table 1, Figure 3). The results of this analysis showed area under the curve (AUROC) of NLR, LDH, albumin, and ferritin was 0.864 ($p < 0.001$), [95% CI (0.762 - 0.966)], 0.829 ($p < 0.001$), [95% CI (0.672 - 0.986)], 0.807 ($p < 0.001$), [95% CI (0.685 - 0.929)], 0.807 ($p < 0.001$), [95% CI (0.665 - 0.948)] respectively. NLR exhibited the largest area under the curve at 0.864, showing that it was the best predictor of severe COVID-19 infection. Likewise, high LDH, high ferritin, and negative albumin were also good predictors of ICU admission due to severe COVID-19 infection (Table 1). The AUROC of other variables (age, WBC count, D-D, Trp, BNP, Lym negative, ALT, PCT, INR, and PT) varied from 0.645 to 0.775, reflecting weaker prognostic performance to assess severe forms of COVID-19 (Table 1, Figure 1).

Cytokines

We further analyzed whether the measured cytokines were predictors of disease severity. Thirteen cytokines were measured on admission up to the time of admission to ICU or discharge from the hospital. Except for IFN-α, IL-23, and IL-33, the mean values of all of the measured cytokines were above the normal cutoff values (Table 3).

Table 1. ROC curve analysis.

			95% CI	
Variables	**AUROC**	**p**	**Lower**	**Upper**
Age	**0.645**	**0.12**	**0.49**	**0.8**
WBC count	**0.646**	**0.118**	**0.463**	**0.829**
Neutrophil	**0.77**	**0.004**	**0.615**	**0.925**
N/L ratio	**0.864**	**0.001**	**0.762**	**0.966**
Procalcitonin	**0.753**	**0.007**	**0.605**	**0.901**
Ferritin	**0.807**	**0.001**	**0.665**	**0.948**
D-D	**0.662**	**0.083**	**0.468**	**0.855**
INR	**0.77**	**0.004**	**0.618**	**0.923**
PT	**0.775**	**0.003**	**0.623**	**0.927**
Troponin	**0.69**	**0.041**	**0.531**	**0.85**
Pro-BNP	**0.71**	**0.024**	**0.557**	**0.863**
ALT	**0.77**	**0.004**	**0.636**	**0.904**
LDH	**0.829**	**0.001**	**0.672**	**0.986**
Lymphocyte-neg	**0.751**	**0.007**	**0.579**	**0.924**
Albumin-neg	**0.807**	**0.001**	**0.685**	**0.929**

WBC - white blood cell, N/L Ratio - neutrophil-lymphocyte ratio, D-D - D-dimer, PT - prothrombin time, INR - international normalizing ratio, pro-BNP - pro B type natriuretic peptide, ALT - alanine aminotransferase, LDH - lactic dehydrogenase, neg - negative.

Measurements were repeated every 48 hours from the beginning. MCP-1 and IL-6 cytokines increased in patients who needed the ICU compared to in non-ICU patients after 4 days admission (Figure 2-3). There were no cytokine measurements in the ICU.

Treatment

The antiviral drugs used were favipiravir, 92 (79.3%), oseltamivir, 7 (6%), a combination of lopinavir and ritonavir, 5 (4.3%), and remdesivir, 1 (0.8%) (Supplementary Table 1). Other medications used were antibiotics, glucocorticoids, tocilizumab, hydroxychloroquine, colchicine, ascorbicacid, convalescent plasma, and low-molecular-weight heparin (Supplementary Table 1). When we evaluated the treatments separately: all ICU patients received favipiravir, 86% corticosteroids, 90% low-weight heparin, and 54% tocilizumab. In contrast, 73% of non-ICU patients received favipiravir, 22% corticosteroids, 56% low-weight heparin, and 12% tocilizumab.

DISCUSSION

Because the clinical findings were not always written correctly in the medical records from which we extracted the data, instead of calculating the severity of the disease as mild, moderate, and severe, we classified the patients who needed to be admitted to an ICU as severe cases. COVID-19 patients who needed ICU admissions were older in age 55 ± 13 vs. 46 ± 15 years ($p < 0.001$), while the mean age of the total patients was 55 ± 16.4 and the mean age of the intensive care patients was 65.7 ± 10.5. The mean age of the patients who died was 68.5 ± 10.5 years. Also, age seems to be an important risk factor for both contracting the disease and the severity of critical illness.

There were disproportionately more men in our cohort (64%), and 21,6% of the males needed the ICU. In contrast, 14,2% of the female cases required intensive care. The epidemiological findings that were reported across different parts of the world indicated higher morbidity and mortality in males than females. Our results also support these observations. This may be due to differences in the immune system between men and women in the fight against COVID-19 [19,20].

Out of all patients, 62.9% and 86% of the patients admitted to the intensive care unit had at least one comorbidity. Only 3 of the patients who were admitted to the ICU did not have any comorbidity. Also, all patients who died had at least one comorbidity. Taken together, it shows that presence of comorbidities like diabetes and hypertension is both a risk for COVID-19 infection and a factor for disease severity [21-23].

The results of our study showed that the most common laboratory findings in patients with COVID-19 were increased WBC, neutrophil, decreased Alb, lymphopenia, N/L ratios, increased ferritin, increased ALT, increased LDH, increased procalcitonin, D-D, INR, and PT.

Patients that needed ICU admission showed a higher WBC (mean: 8,811 vs. 7,043, $p < 0.013$) and neutrophil (mean: 7,486 vs. 4,475, $p < 0.001$) count compared with

Table 2. Cytokine levels of patients on admission.

	IL-1β (pg/mL) cutoff < 4.5	IFN-α (pg/mL) cutoff < 21.2	IFN-γ (pg/mL) cutoff < 3.5	TNF-α (pg/mL) cutoff < 4.7	MCP-1 (pg/mL) cutoff < 231.1	IL-6 (pg/mL) cutoff < 4.3	IL-8 (pg/mL) cutoff < 16.8	IL-10 (pg/mL) cutoff < 2.7	IL12p-70 (pg/mL) cutoff < 2.3	IL-17A (pg/mL) cutoff < 0.0	IL-18 (pg/mL) cutoff < 120.5	IL-23 (pg/mL) cutoff < 13.4	IL-33 (pg/mL) cutoff < 30.6
All patients n: 65 mean (SD)	**17.99 (37.78)**	**15.97 (22.69)**	**36.85 (82.65)**	**12.18 (18.73)**	**468.98 (352.19)**	**172.05 (443.44)**	**68.72 (69.93)**	**71.43 (122.89)**	**3.02 (7.02)**	**6.08 (17.49)**	**678.77 (476.59)**	**9.18 (9.09)**	**26.17 (32.84**
Non-ICU n: 49 mean (SD)	**19.29 (42.34)**	**16.39 (23.17)**	**30.08 (44.02)**	**12.19 (19.83)**	**436.43 (305.09)**	**86.36 (168.78)**	**67.92 (73.77)**	**59.39 (66.98)**	**3.46 (7.91)**	**6.84 (19.83)**	**637.77 (485.05)**	**9.54 (9.71)**	**29.84 (35.44)**
ICU n: 10 mean (SD)	**12.57 (16.77)**	**13.97 (23.00)**	**16.49 (29.08)**	**9.32 (15.86)**	**433.22 (328.55)**	**291.78 (524.09)**	**58.43 (56.08)**	**126.84 (278.90)**	**0.64 (0.81)**	**1.67 (2.65)**	**624.34 (361.52)**	**6.16 (7.31)**	**12.63 (14.94)**
Death n: 5 mean (SD)	**29.88 (25.34)**	**11.04 (11.14)**	**134.78 (264.90)**	**15.65 (14.48)**	**946.81 (603.23)**	**808.75 (1,243.82)**	**126.71 (54.25)**	**87.85 (52.37)**	**3.19 (4.42)**	**8.23 (10.10)**	**1,103.50 (491.98)**	**11.91 (6.09)**	**15.66 (32.27)**

ICU - intensive care unit, IL - interleukin, IFN - interferon.

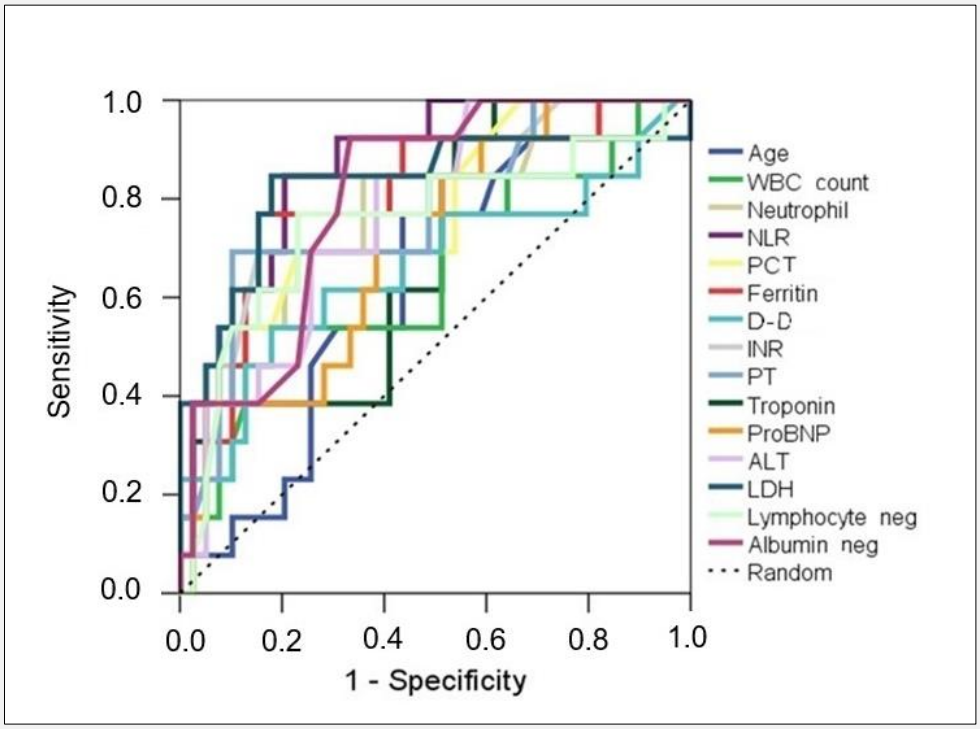

Figure 1. ROC curves for the diagnostic power of each variable.

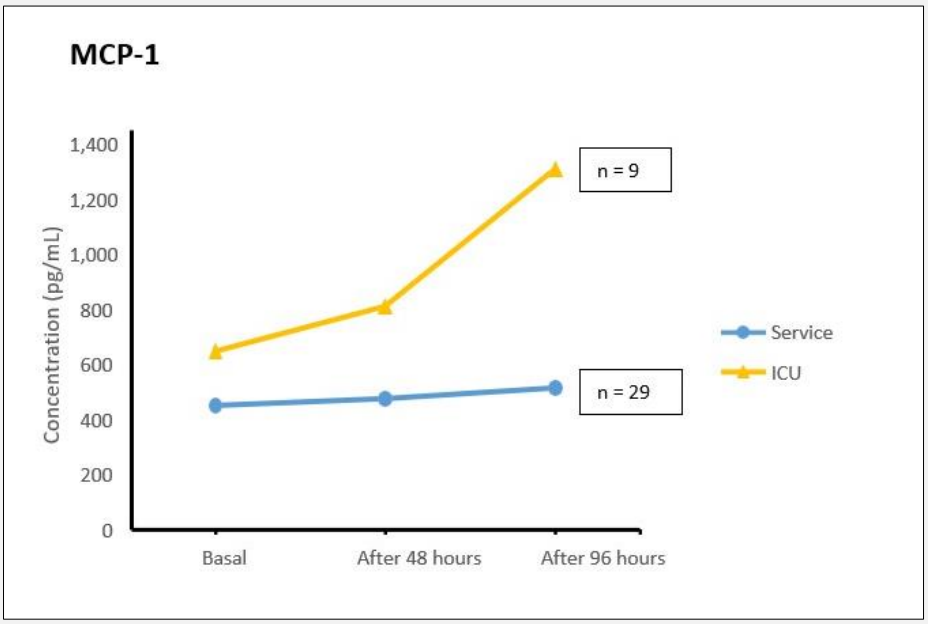

Figure 2. MCP-1 levels at 48-hour intervals.

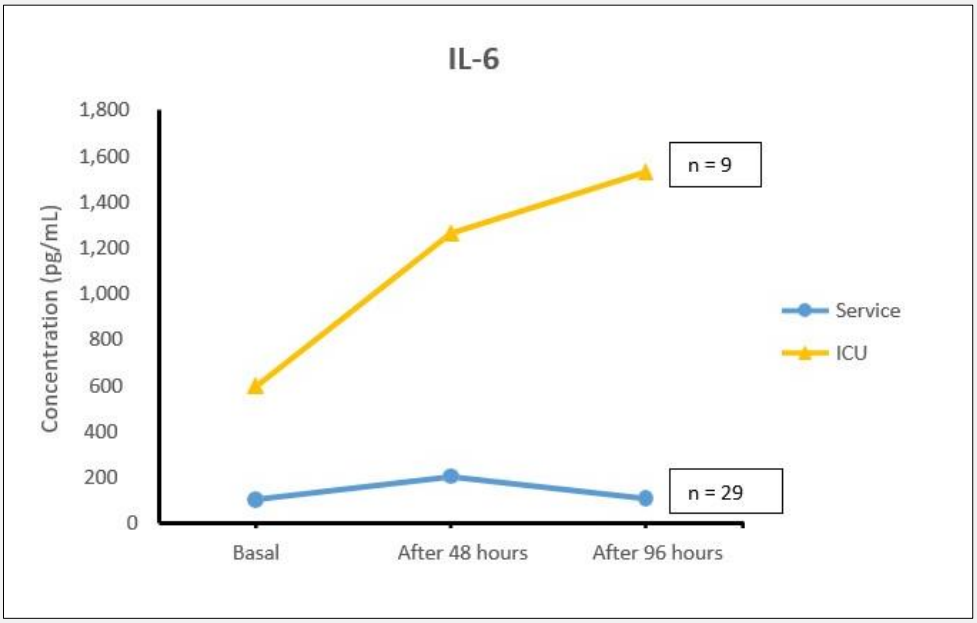

Figure 3. IL-6 levels at 48-hour intervals.

non-ICU patients (Supplementary Table 2). Recently it was suggested that enhanced neutrophil infiltration and the release of neutrophil extracellular traps can induce necroinflammation that contributes to the higher mortality of COVID-19 in patients with underlying comorbidities [22].

Patients that needed ICU admission showed a lower lymphocyte count compared with non-ICU patients (mean: 967 vs. 1,458, $p < 0.003$) (Supplementary Table 2). One of the key features of COVID-19 infection is lymphopenia, which correlates with clinical severity [2]. Additionally, several studies have reported that lymphopenia is suggestive of a critical factor accounting for severity and mortality. At the same time, calculated N/L ratios were higher in intensive care patients compared to non-intensive care patients (mean: 9.7 vs. 4.3, $p < 0.001$) (Supplementary Table 2). It was reported that the neutrophil-to-lymphocyte ratio can be utilized as a biomarker to predict how the infection will progress. It has been proven that NLR equal to 5 is a critical value for the assessment of disease severity in patients with COVID-19 [9].

There were no significant changes in RBC, Hb, and creatinine levels in both groups.

ALT was higher (mean: 66 vs. 41, $p < 0.0007$) and albumin was lower (mean: 2.9 vs. 3.6, $p < 0.001$) in ICU patients, compared to non-ICU patients that might indicate hepatic injury. It is not known whether the increases in ALT and AST levels during the course of COVID-19 are the direct effect of the virus, the toxic effect of the drugs used, or part of the multiple organ dysfunction in COVID-19 [23].

Ferritin increased in both groups, but this increase was significantly higher in ICU patients than in non-ICU patients (1,011 vs. 442, $p < 0.001$) (Supplementary Table 2). The importance of ferritin as an inflammatory marker is well recognized. It was reported that high ferritin levels are a poor prognostic factor and contribute to the cytokine storm associated with fatal outcomes in COVID-19 [22].

Patients that needed ICU admission showed a higher LDH compared with non-ICU patients (mean: 663 vs. 376, $p < 0.001$) (Table 4). Lactate dehydrogenase is an enzyme that converts lactate to pyruvate and so contributes to energy production. It can be found in virtually every cell in the body, with the heart, liver, lungs, muscles, kidneys, and blood cells having the greatest concentrations. Increased LDH levels indicated that multiple organ damage may have a bigger role in deciding clinical outcomes in patients with COVID-19 [20]. LDH is an inflammatory marker that may be used to determine if tissue damage is acute or persistent. LDH levels were significantly higher in severe patients than in non-severe patients. Another study showed that the LDH level on admission negatively correlated with survival days [23].

When the means of all patients were calculated, we saw that the CRP values increased in COVID-19 infection

(mean: 4.8 ± 6 mg/dL, N < 0.5 mg/dL) (Table 1), but there was no significant difference between the values in ICU patients and non-ICU patients.

Coagulation tests such as D-dimer, INR, and PT were significantly increased in ICU patients (D-dimers mean: 1,855 vs. 442, $p < 0.014$; INR mean: 1.2 vs. 1.1, $p < 0.002$; and PT mean: 15.6 vs. 14.2, $p < 0.002$, respectively) (Supplementary Table 2). Likewise, there are significant increases in troponin and Pro-BNP levels in ICU patients ($p < 0.004$, $p < 0.004$, and $p < 0.001$, respectively). Patients that needed ICU admission showed a significant increase in procalcitonin levels compared with non-ICU patients (mean: 0.4 vs. 0.08, $p < 0.00$) (Supplementary Table 2).

Thirteen cytokines thought to be associated with inflammatory events were measured. When the patients were hospitalized, the serum values of all these cytokines were above normal. In patients who died later, IL-1β, IFN-γ, MCP-1, IL-6, IL-8, IL-10, and IL-18 levels were significantly higher at the beginning, even if statistical calculations were not made, because the numbers were low (Table 2).

Measurements were repeated every 48 hours. IFN-α, IFN-γ, and IL-10 levels decreased in repeated measurements: these cytokines do not appear to be positive indicators of disease severity in our study. At the 96th hour, serum levels of IL-1β, TNF-α, IL-8, IL-12p70, IL-17A, IL-18, IL-23, and IL-33 cytokines increased in both non-ICU and in ICU patients. However, MCP-1 and IL-6 levels were found to be significantly higher in patients who needed ICU compared to patients who did not (Figure 2 and 3).

MCP-1 (Monocyte chemoattractant protein-1) plays a vital role in the pathogenesis of diseases characterized by monocyte infiltration, such as psoriasis, rheumatoid arthritis, and atherosclerosis, being involved in the recruitment of monocytes [24,25]. MCP-1 has also been shown to contribute to the pathogenesis of COVID -19 [24]. MCP-levels, like some other cytokines, were found to be high in patients admitted to intensive care unit [26]. Another study showed that IP-10 and MCP-1 levels were elevated in critically ill patients and suggested that these cytokines may be biomarkers of disease severity in COVID-19 infection [24].

IL-6 is one of the most important cytokines. It is a highly pleotropic cytokine that functions in various biological systems and almost all tissues in the body. IL-6 signaling is initiated by the binding of IL-6 to IL-6R and gp130, a second transmembrane protein that acts as a signal transducer of IL-6. Although IL-6R is restrictedly expressed in hepatocytes, monocytes, and lymphocytes, gp130 is ubiquitously present, explaining the pleotropic functions of IL-R. In COVID-19 patients, IL-6 is found at elevated levels, especially in severe and critically ill patients, and is believed to lead to multiple organ damage [27-29].

In our study, the increases in IL-6 and MCP-1 levels, which increase in parallel with disease severity, seem to be consistent with the data of other researchers.

There are reports that claim smoking protects from COVID 19 [30]. On the contrary, there are studies showing that active smoking increases the risk of severe COVID-19 [31]. Most reports that claim that smoking protects from COVID 19 infection have methodological problems, including selection bias and misclassification bias [31,32]. In our study, smoking status was in the form, with 7.7% current smokers and 3.4% ex-smokers. We do not interpret the low rate of smoking in our study as a protective effect. In retrospective studies, there are often deficiencies in the records of patient data. We think that smokers were underrepresented in our study. However, we also think that prospective cohort studies are needed to clarify the causal relationship between smoking and COVID-19.

The ROC analysis is a valuable tool to evaluate diagnostic tests and predictive models. In our study, according to the results of the ROC analysis, a high NLR and a high LDH were the best predictors of severe COVID-19.

It is worth noting that our study has some limitations. First, sample size was small for some parameters such as cytokines; larger numbers are needed for statistical comparisons. Second, given its retrospective observational design, there is a possibility of information bias. Third, although we analyzed laboratory and demographic risk factors, the causality relationships were not well examined due to small sample sizes in some groups. Fourth, these results are from the period before the introduction of COVID-19 vaccines; related to the natural course of the infection. Vaccination might produce different findings.

CONCLUSION

Patients with ICU admission showed a distinct clinical demographic as well as laboratory features when compared to patients who did not need ICU admission. These include the elder age group, male gender, and patients with increased ferritin, increased D-dimer, procalcitonin, increased ALT, lymphopenia, increased WBC and neutrophil count, N/L ratios, increased LDH, and cytokines, such as MCP-1 and IL-6, with increased serum levels. These results should be considered when interpreting laboratory parameters in patients with COVID-19. Because these findings may reflect multiple organ injuries, the patients require proper management and, if need be, should be transferred to the intensive care unit.

HIGHLIGHTS

- Clinical and laboratory findings are important in evaluating the need for ICU admission.
- High NLR ratios and LDH levels and low Alb levels are the highest prognostic power in terms of disease severity.

- Increased MCP-1 and IL-6 levels should be taken into consideration in predicting the need for ICU admission.

Acknowledgment:
We would like to thank Prof Dr. Hasan Yazici for his critical reading, Prof Dr. Canan Agalar and Prof Dr. Gulderen Y. Demirel for their assistance in developing the methodology, Dr. Ozgur Albayrak and Dr. Burak Sarikaya for their laboratory assistance, and Prof Dr. Emel Timucin and Dr. Omer Uysal for their assistance in the statistical evaluation.

Ethical Approval:
Research data has been obtained following the approval of the official authorities. Artificial intelligence supported technologies were not used in this study. Since this study was conducted during the Covid-19 pandemic, the only approval was obtained from the Ministry of Health in accordance with the current legislation at that time (the relevant document has been uploaded under the title of ethics committee approval).

Declaration of Interest:
None.

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